

**REMARKS**

Claims 1, 4-8, 11, 13-16, 18-22, 28-30, 36-44, 46, 48, 50-59, 61-66, 70-72, 74, 76-78, 83, 85, 88, 91-95, 98-100 and 133-137 are pending. Claims 1, 4, 70, 74 and 137 have been amended. Claims 2, 3, 9-12, 17, 23-27, 31-35, 45, 47, 49, 60, 67-69, 73, 75, 79-82, 84-87, 89, 90, 96, 97, 101-132 and 138-139 have been cancelled. No new matter has been introduced by way of these amendments and support for them can be found in the claims as originally filed. Reconsideration of the pending claims in view of the amendments above and remarks below is respectfully requested.

**Sequence listing**

Due to errors found in the previously submitted Sequence Listing, applicants submit herewith a substitute paper copy of the Sequence Listing, pages 1-25, and substitute computer readable form (labeled "CRF") of the Sequence Listing in CD-R format, in compliance with 37 C.F.R. §1.821(c), and §1.825(a) and (b). The substitute sheets of the Sequence Listing and the substitute computer readable form labeled "CRF" submitted herewith, in accordance with 37 C.F.R. §1.825(a) and (b), respectively, are the same and contain no new matter. Accordingly, entry of the substitute Sequence Listing into the above-captioned case is respectfully requested. Claim 137 was amended to include a SEQ ID number which was inadvertently omitted at the time of filing.

**Rejection Under 35 U.S.C. § 112, Second Paragraph**

Claims 1, 4-8, 11, 13-16, 18-22, 28-30, 36-44, 48, 50, 51-59, 61-66, 70-72, 74, 76-78, 83, 85, 88, 91-95, 98-100, and 133-137 were rejected under 35 U.S.C. § 112, second paragraph for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Office rejected claim language noting mutations in the hexadactyl zinc finger protein's DNA binding site relative to a wild type protein. Applicants have deleted this claim language to clarify the subject matter regarded as the invention. Accordingly this rejection should be withdrawn.

Rejection Under 35 U.S.C. § 103

Claims 1, 4-8, 13-16, 19-20, 22, 28-29, 36-43, 48, 50-59, 70, and 133-137 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cox, III *et al.* (U.S. Patent No. 6,534,261; herein after “Cox”) in view of Segal *et al.* (Proc. Natl. Acad. Sci. USA (1999) 96:2758-2763; hereinafter “Segal”).

To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Second, there must be a reasonable expectation of success found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Third, the prior art must reference must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974).

The Office’s proposed combination of Cox and Segal fails to establish a *prima facie* case of obviousness because one of ordinary skill in the art would not have been motivated to combine the two references. It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, (Fed. Cir. 1983); MPEP § 2145. Here, Cox teaches that the design of their ZFPs contain one or more “D-able” sites. Cox, col. 15, lines 42-48. Cox defines a “D-able site” as

“[A] region of a target site that allows an appropriately designed single zinc finger to bind to four bases rather than three of the target site. Such a zinc finger binds to a triplet of bases on one strand of a double-stranded target segment (target strand) and a fourth base on the other strand (see FIG. 2 of copending application entitled "Selection of Sites for Targeting by Zinc Finger Proteins and Methods of Designing Zinc Finger Proteins to Bind to Pre-selected Sites," U.S. Ser. No. 09/229,007, filed Jan. 12, 1999.” Cox, col. 15, lines 61-67.

Segal, on the other hand, teaches the binding of an 18 base pair sequence. See, e.g., Segal, abstract, page 2758. Because the two references teach such fundamentally different target sites, one of ordinary skill in the art would not be motivated to combine these two references.

In view of the discordance existing between these references, Applicants submit that no *prima facie* case of obviousness has been articulated and thus the present rejection should be withdrawn.

Claims 1, 4-8, 13-16, 19-20, 22, 28-29, 36-43, 48, 50-59, 61-66, 70, and 133-137 were also rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cox in view of Segal as it applies to claims 1, 4-8, 13-16, 19-20, 22, 28-29, 36-43, 48, 50-59, 70, and 133-137 above, and further in view of the prior art. The Office alleged that while Cox and Segal do not teach the inclusion of a transit peptide in the plant expression vector, the inclusion of such a peptide was well known at the time the present application was filed.

In this rejection the Office argued that claims 61-66 were also obvious in view of Cox, Segal and other reference and alleged that “chloroplast, mitochondria, and nucleus transit peptides were well known and widely used at the time Applicant’s invention was filed.” Office Action, page 9, second paragraph. This additional rejection is flawed for the reasons discussed above. Specifically, one of ordinary skill in the art would not have been motivated to combine or modify the teachings of Cox and Segal to achieve the claimed invention. As such, the knowledge of the art regarding chloroplasts, mitochondria or nuclear transit peptides does nothing to cure the defects of the Office’s obviousness rejection. Accordingly, the present rejection should be withdrawn.

Claims 1, 4-8, 11, 13-16, 19-22, 28-30, 36-44, and 133-137 were also rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over de Pater, *et al.* (Nucleic Acids Research (1996) 24(23):4624-4631; hereinafter “de Pater”) in view of Barbas, *et al.* (WO 98/54311; hereinafter “Barbas”). As noted above, one of the three prongs of a *prima facie* case of obviousness requires that the cited references, taken as a whole, teach all the limitations of the claimed invention. Here, neither de Pater nor Barbas, whether taken alone or in combination teach or suggest a synthetic zinc finger protein which targets a nucleotide sequence comprising 18 consecutive nucleotides of the formula (GNN)<sub>6</sub>, wherein N is any one of A, T, C or G wherein the zinc finger protein is a hexadactyl zinc finger protein.

Regarding the ability of the proteins disclosed in Barbas to bind to (GNN)<sub>6</sub> sequences, the Office noted that two proteins taught in the reference could bind to such sequences. Without acquiescing to this point, Applicants note that the formula (GNN)<sub>6</sub> is not taught or even suggested in either reference. Thus, the cited references cannot be construed to teach this feature, except perhaps by invoking the doctrine of inherency, which is not available to the Office when crafting an obviousness rejection. In view of this, the present references do not constitute a *prima facie* case of obviousness. Accordingly, the present rejection should be withdrawn.

The Office Action on page 12 states that claims 1, 4-8, 13-16, 19-22, 28-30, 36-44, 51-59, 61-66, 70, and 133-137 were also rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cox in view of Segal as it applies to claims 1, 4-8, 11, 13-16, 17, 19-22, 28-30, 36-44, 55-59, 70, and 133-137 above, and further in view of the prior art. The rejection goes on to state the de Pater and Barbas were discussed above in the action and that one of ordinary skill in the art would have considered the inclusion of transit peptides obvious, even though neither de Pater nor Barbas teach the use of such peptides. Applicants are not clear as to which references the Office is citing in connection with this rejection and request clarification. Nevertheless, Applicants note that the art's teachings regarding transit peptides do not cure the deficiencies in Cox, Segal, de Pater or Barbas. Thus, the present rejection should be withdrawn.

Claims 1, 4-8, 11, 13-16, 19-22, 28-30, 36-44, and 133-137 were also rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yanagisawa *et al.* (The Plant Cell (1998) 10:75-89) in view of Barbas *et al.* The Barbas reference is discussed above. The Yanagisawa reference discloses a binding site of AAAGG for Dof1 which does not appear to meet the limitations of the claims. Here, neither Yanagisawa *et al.* nor Barbas, whether taken alone or in combination teach or suggest a synthetic zinc finger protein which targets a nucleotide sequence comprising 18 consecutive nucleotides of the formula (GNN)<sub>6</sub>, wherein N is any one of A, T, C or G wherein the zinc finger protein is a hexadactyl zinc finger protein. In part because Yanagisawa teaches a different binding site for Dof1, one of ordinary skill in the art would not have been motivated to combine it with Barbas to achieve the claimed invention.

Claims 1, 4-8, 13-16, 19-22, 28-30, 36-44, 51-59, 61-66, 70, and 133-137 were also rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yanagisawa in view of BARBAS as it applies to 1, 4-8, 11, 13-16, 17, 19-22, 28-30, 36-44, and 133-137 above, and further in view of the prior art. The Office alleged that one of ordinary skill in the art would have considered the use of transit peptides obvious and thus would have combined them with the teachings of Yanagisawa in view of Barbas to achieve the claimed invention. As discussed above, the different binding site of Dofl would have discouraged those of ordinary skill in the art from combining the teachings of Yanagisawa with those of Barbas. Teachings regarding transit peptides do nothing to overcome this deficiency. As such, these references fail to articulate a prima facie case of obviousness.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 278012001420. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

By 

James J. Mullen III, Ph.D.

Registration No.: 44,957

MORRISON & FOERSTER LLP  
12531 High Bluff Drive, Suite 100  
San Diego, California 92130  
(858) 720-7940